STIC-Biotech/ChemLib

78490 Seq

79080 Text

From: Wessendorf,Teresa
Sent: Wednesday, October 23, 2002 11:00 AM
To: STIC-Biotech/ChemLib
Subject: FW: 09/463,098

Sorry, I forgot to give the different amino acids with X s in several positions of Sq. ID. 39. X at position 3 is T, R, H; at position 11 X is R, h; at position 18 X is S, G, R; position 22 is P, L, S, Q; pos. 24 is A,P,S. The specific peptide is Seq. ID. 1.

-----Original Message-----
From: Wessendorf,Teresa
Sent: Wednesday, October 23, 2002 10:18 AM
To: STIC-Biotech/ChemLib
Subject: 09/463,098

Please search ~~SEq. ID.~~ 39 with the terms Hypervariable region 1 Variants of E2 protein Hepatitis C. Also, please do inventor search.
Txs.
T. Wessendorf
Art Unit 1639
Rm. 2B17
MailRm. 3B01
308-3967

09/463098

U.S. DEPARTMENT OF COMMERCE
Patent and Trademark Office

SEARCH REQUEST FORM

Requestor's Name: _____ Serial Number: _____

Date: _____ Phone: _____ Art Unit: _____

Search Topic:

Please write a detailed statement of search topic. Describe specifically as possible the subject matter to be searched. Define any terms that may have a special meaning. Give examples or relevent citations, authors, keywords, etc., if known. For sequences, please attach a copy of the sequence. You may include a copy of the broadest and/or most relevent claim(s).

STAFF USE ONLY

Date completed: 10/30

Searcher: D Silverberg 308-4294

Terminal time: 549 | 1394

Elapsed time: 10 | 19

CPU time: _____

Total time: _____

Number of Searches: _____

Number of Databases: 5 | 6

Search Site

_____ STIC

✓ CM-1 (CM3)

_____ Pre-S

Type of Search

_____ N.A. Sequence

6 A.A. Sequence

_____ Structure

_____ Bibliographic

Vendors

✓ IG Quest

✓ STN (CAS)

_____ Dialog

_____ APS

_____ Geninfo

_____ SDC

_____ DARC/Questel

✓ Other GCG

5-1-98

PTO-1590 (9-90)

Wessendorf 09/463,098

=> d his 1

(FILE 'MEDLINE, HCAPLUS, BIOSIS, EMBASE, SCISEARCH, AGRICOLA' ENTERED AT 12:57:01 ON 30 OCT 2002)

L20 11 S L14 OR L19

=> d que l20

L1 108 SEA FILE=REGISTRY QT[TRH]TVGGQAS[RH]QASSLT[SGR]LFS[PLSQ]G[APS]K QN/SQSP
L2 1 SEA L1
L3 427 SEA NICOSIA A?/AU
L4 231 SEA LAHM A?/AU
L5 605 SEA TRAMONTANO A?/AU
L6 993 SEA CORTESE R?/AU
L7 1825 SEA HYPERVARIABLE(5A) REGION#(5A) 1
L8 6534192 SEA VARIANT# OR STRAIN# OR MUTANT? OR TYPE
L9 117454 SEA HEPATITIS(3A) C# OR HCV#
L10 1 SEA L2 AND ((L3 OR L4 OR L5 OR L6))
L11 1 SEA L2 AND ((L7 OR L8 OR L9))
L12 169829 SEA "E2"
L13 1 SEA L2 AND L12
L14 1 SEA L2 OR L10 OR L11 OR L13
L15 21 SEA ((L3 OR L4 OR L5 OR L6)) AND (L7(5A) L12)
L16 9 DUP REM L15 (12 DUPLICATES REMOVED)
L17 158 SEA L7(5A) L12(5A) L9
L18 3 SEA L17(5A) L8
L19 11 SEA L16 OR L18
L20 11 SEA L14 OR L19

=> d ibib abs l20 1-11

L20 ANSWER 1 OF 11 MEDLINE
ACCESSION NUMBER: 2001566748 MEDLINE
DOCUMENT NUMBER: 21526361 PubMed ID: 11672825
TITLE: Hypervariable region 1 of hepatitis C virus: immunological decoy or biologically relevant domain?.
AUTHOR: Mondelli M U; Cerino A; Segagni L; Meola A; Cividini A; Silini E; **Nicosia A**
CORPORATE SOURCE: Laboratori di Ricerca, Area Infettivologica and Istituto di Clinica delle Malattie Infettive, IRCCS Policlinico San Matteo, University of Pavia, Via Taramelli 5, 27100 Pavia, Italy.. m.mondelli@smatteo.pv.it
SOURCE: ANTIVIRAL RESEARCH, (2001 Nov) 52 (2) 153-9. Ref: 34
Journal code: 8109699. ISSN: 0166-3542.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200204
ENTRY DATE: Entered STN: 20011024
Last Updated on STN: 20020405
Entered Medline: 20020404

AB The **hypervariable region 1** (HVR1) of the **E2** protein of hepatitis C virus (HCV) is highly heterogeneous and is responsible for significant inter- and intra-individual variation of the infecting virus, which may represent an important pathogenetic

Search completed by David Schreiber 308-4292

mechanism leading to escape and persistent infection. Moreover, a binding site for neutralizing antibodies (Ab) has been allegedly identified in this region. Prospective studies of serological responses to synthetic oligopeptides derived from HVR1 sequences of patients with acute and chronic HCV infection showed extensive serological cross-reactivity for unrelated HVR1 peptides in the majority of the patients. A significant correlation was found between HVR1 sequence variation, and intensity, and cross-reactivity of humoral immune responses providing strong evidence in support of the contention that HCV variant selection is driven by the host immune pressure. Monoclonal Ab (mAb) generated following immunization of mice with peptides derived from natural HVR1 sequences also showed cross-reactivity for several HVR1 sequences attesting to the existence of conserved amino acid motifs among different variants. These findings suggest that it is possible to induce a broadly cross-reactive immune response to HVR1 and that this mechanism can be used to generate protective immunity for a large repertoire of HCV variants.

L20 ANSWER 2 OF 11 MEDLINE
ACCESSION NUMBER: 2001527391 MEDLINE
DOCUMENT NUMBER: 21448718 PubMed ID: 11564805
TITLE: Monoclonal antibodies with broad specificity for hepatitis C virus hypervariable region 1 variants can recognize viral particles.
AUTHOR: Cerino A; Meola A; Segagni L; Furione M; Marciano S; Triyatni M; Liang T J; **Nicosia A**; Mondelli M U
CORPORATE SOURCE: Laboratori di Ricerca-Area Infettivologica, IRCCS Policlinico San Matteo, University of Pavia, Via Taramelli 5, 27100 Pavia, Italy.
SOURCE: JOURNAL OF IMMUNOLOGY, (2001 Oct 1) 167 (7) 3878-86. Journal code: 2985117R. ISSN: 0022-1767.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200112
ENTRY DATE: Entered STN: 20011001
Last Updated on STN: 20020122
Entered Medline: 20011204

AB The **hypervariable region 1** (HVR1) of the **E2** protein of hepatitis C virus (HCV) is a highly heterogeneous sequence that is promiscuously recognized by human sera via binding to amino acid residues with conserved physicochemical properties. We generated a panel of mAbs from mice immunized with HVR1 surrogate peptides (mimotopes) affinity-selected with sera from HCV-infected patients from a phage display library. A high number of specific clones was obtained after immunization with a pool of nine mimotopes, and the resulting mAbs were shown to recognize several 16- and 27-mer peptides derived from natural HVR1 sequences isolated from patients with acute and chronic HCV infection, suggesting that HVR1 mimotopes were efficient antigenic and immunogenic mimics of naturally occurring HCV variants. Moreover, most mAbs were shown to bind HVR1 in the context of a complete soluble form of the E2 glycoprotein, indicating recognition of correctly folded HVR1. In addition, a highly promiscuous mAb was able to specifically capture bona fide viral particles (circulating HCV RNA) as well as rHCV-like particles assembled in insect cells expressing structural viral polypeptides derived from an HCV 1a isolate. These findings demonstrate that it is possible to induce a broadly cross-reactive clonal Ab response to multiple HCV variants. In consideration of the potentially important role of HVR1 in virus binding to cellular receptor(s), such a mechanism could be exploited

for induction of neutralizing Abs specific for a large repertoire of viral variants.

L20 ANSWER 3 OF 11 MEDLINE
ACCESSION NUMBER: 1999350394 MEDLINE
DOCUMENT NUMBER: 99350394 PubMed ID: 10421665
TITLE: Antibody responses to hepatitis C virus hypervariable region 1: evidence for cross-reactivity and immune-mediated sequence variation.
AUTHOR: Mondelli M U; Cerino A; Lisa A; Brambilla S; Segagni L; Cividini A; Bissolati M; Missale G; Bellati G; Meola A; Bruniercole B; **Nicosia A**; Galfre G; Silini E
CORPORATE SOURCE: Laboratori di Ricerca-Area Infettivologica, Istituto di Clinica delle Malattie Infettive, Pavia, Italy.
SOURCE: HEPATOLOGY, (1999 Aug) 30 (2) 537-45.
Journal code: 8302946. ISSN: 0270-9139.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199908
ENTRY DATE: Entered STN: 19990820
Last Updated on STN: 19990820
Entered Medline: 19990812

AB Sequence heterogeneity of hepatitis C virus (HCV) is unevenly distributed along the genome, and maximal variation is confined to a short sequence of the HCV second envelope glycoprotein (**E2**), designated **hypervariable region 1** (HVR1), whose biological function is still undefined. We prospectively studied serological responses to synthetic oligopeptides derived from HVR1 sequences of patients with acute and chronic HCV infection obtained at baseline and after a defined follow-up period. Extensive serological cross-reactivity for unrelated HVR1 peptides was observed in the majority of the patients. Antibody response was restricted to the IgG1 isotype and was focused on the carboxyterminal end of the HVR1 region. Cross-reactive antibodies could be readily elicited following immunization of mice with multiple antigenic peptides carrying HVR1 sequences derived from our patients. The vigor and heterogeneity of cross-reactive antibody responses were significantly higher in patients with chronic hepatitis compared with those with acute hepatitis and in patients infected with HCV type 2 compared with patients infected with other viral genotypes (predominantly type 1), which suggest that higher time-related HVR1 sequence diversification previously described for type 2 may result from immune selection. The finding of a statistically significant correlation between HVR1 sequence variation, and intensity, and cross-reactivity of humoral immune responses provided stronger evidence in support of the contention that HCV variant selection is driven by the host's immune pressure.

L20 ANSWER 4 OF 11 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2002:449524 HCAPLUS
DOCUMENT NUMBER: 137:32051
TITLE: **HCV** vaccines comprising epitopes of **hypervariable 1 region** of envelope protein **E2** of different **HCV strains**
INVENTOR(S): Allain, Jean-Pierre; Li, Chengyao; Piccolella, Enza
PATENT ASSIGNEE(S): UK
SOURCE: PCT Int. Appl., 52 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002045743	A2	20020613	WO 2001-GB5421	20011207
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 2002022139	A5	20020618	AU 2002-22139	20011207

PRIORITY APPLN. INFO.: GB 2000-30102 A 20001209
GB 2000-30789 A 20001218
WO 2001-GB5421 W 20011207

AB HCV vaccines are described which are capable of raising antibodies and/or helper T lymphocytes and/or cytotoxic T lymphocytes which are cross-reactive to the **hypervariable 1** (HVR **1**) **region** of the envelope protein **E2** of different **HCV strains**. A preferred therapeutic vaccine for treatment of chronic HCV infection comprises a plurality of different groups of peptides, each peptide comprising a different known HVR 1 C-terminal sequence or a different consensus of known HVR 1 C-terminal sequences. The different groups of peptides are sequentially administered (preferably at intervals of 15-21 days) to raise antibodies, helper t lymphocytes, and cytotoxic T lymphocytes which are cross-reactive to the HVR 1 region(s) of the chronically infecting HCV strain(s). methods of selecting peptides for use in such vaccines are also described.

L20 ANSWER 5 OF 11 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:894447 HCAPLUS
DOCUMENT NUMBER: 136:215089
TITLE: Mimotopes of the hyper variable region 1 of the hepatitis C virus induce cross-reactive antibodies directed against discontinuous epitopes
AUTHOR(S): Roccasecca, Rosamaria; Folgori, Antonella; Ercole, Bruno Bruni; Puntoriero, Giulia; **Lahm, Armin**; Zucchelli, Silvia; Tafi, Rosalba; Pezzanera, Monica; Galfre, Giovanni; **Tramontano, Anna**; Mondelli, M. U.; Pessi, Antonello; **Nicosia, Alfredo**; **Cortese, Riccardo**; Meola, Annalisa
CORPORATE SOURCE: Istituto di Ricerche di Biologia Molecolare "P. Angeletti", Pomezia, Rome, 00040, Italy
SOURCE: Molecular Immunology (2001), 38(6), 485-492
CODEN: MOIMD5; ISSN: 0161-5890
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Hepatitis C virus (HCV) is a major cause worldwide of chronic hepatitis, liver cirrhosis and hepatocellular carcinoma, and the development of an effective vaccine represents a high priority goal. The hyper variable region 1 (HVR1) of the second envelope protein (E2) of HCV contains a

principal neutralizing determinant, but it is highly variable among different isolates and it is involved in the escape from host immune response. To be effective, a vaccine should elicit a cross-reacting humoral response against the majority of viral variants. We show that it is possible to achieve a broadly cross-reactive immune response in rabbits by immunization with mimotopes of the HVR1, selected from a specialized phage library using HCV patients' sera. Some of the cross-reacting anti-mimotope antibodies elicited in rabbits, recognize discontinuous epitopes in a manner similar to those induced by the virus in infected patients.

REFERENCE COUNT: 21 THERE ARE 21 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L20 ANSWER 6 OF 11 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:803321 HCAPLUS
DOCUMENT NUMBER: 136:100164
TITLE: A 385 insertion in the hypervariable region 1 of hepatitis C virus E2 envelope protein is found in some patients with mixed cryoglobulinemia type 2
AUTHOR(S): Gerotto, Martina; Dal Pero, Francesca; Loffreda, Stefano; Bianchi, Francesco B.; Alberti, Alfredo; Lenzi, Marco
CORPORATE SOURCE: Dipartimento di Medicina Clinica e Sperimentale, University of Padua, Padua, 35128, Italy
SOURCE: Blood (2001), 98(9), 2657-2663
CODEN: BLOOAW; ISSN: 0006-4971
PUBLISHER: American Society of Hematology
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Chronic hepatitis C virus (HCV) infection has been assocd. with development of mixed cryoglobulinemia type 2 (MC2), a lymphoproliferative disorder characterized by B cell monoclonal expansion and IgM/k cryoprecipitable Ig prodn. A short sequence (codons 384-410) of the HCV E2 protein, which has the potential to promote B cell proliferation, was investigated in 21 patients with HCV-related MC2 and in a control group of 20 HCV carriers without MC2. In 6 of the 21 (29%) patients with MC2, all the clones isolated from plasma, peripheral blood mononuclear cells, and liver showed sequence length variation compared with the hypervariable region 1 (HVR1) consensus sequence; 5 patients had an insertion at codon 385, and 1 patient had a deletion at codon 384. Inserted residues at position 385 were different within and between patients. No such mutations were obsd. in any of the HVR1 clones from control patients without MC2, and the difference between the 2 groups was statistically significant (P =.02). Anal. of 1345 HVR1 sequences obtained from GenBank strongly supported the conclusion that the obsd. insertions and deletion represent a rare event in HCV-infected patients, suggesting that they are significantly assocd. with MC2. The phys. and chem. profiles of the 385 inserted residues detected in the MC2 patients were consistent with the possibility that these mutations, which occurred in a region contg. immunodominant epitopes for neutralizing antibodies and binding sites for B lymphocytes, may be selected by functional constraints for interaction with host cells.

REFERENCE COUNT: 26 THERE ARE 26 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L20 ANSWER 7 OF 11 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:223565 HCAPLUS
DOCUMENT NUMBER: 135:302457
TITLE: Mimotopes of the hepatitis C virus hypervariable

region 1, but not the natural sequences, induce cross-reactive antibody response by genetic immunization

AUTHOR(S): Zucchelli, Silvia; Roccasecca, RosaMaria; Meola, Annalisa; Ercole, Bruno Bruni; Tafi, Rosalba; Dubuisson, Jean; Galfre, Giovanni; **Cortese, Riccardo; Nicosia, Alfredo**

CORPORATE SOURCE: Istituto di Ricerche di Biologia Molecolare P. Angeletti, Rome, 00040, Italy

SOURCE: Hepatology (Philadelphia, PA, United States) (2001), 33(3), 692-703
CODEN: HPTLD9; ISSN: 0270-9139

PUBLISHER: W. B. Saunders Co.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The hypervariable region 1 (HVR1) of the putative envelope protein E2 of hepatitis C virus (HCV) contains a principal neutralization epitope, and anti-HVR1 antibodies have been shown to possess protective activity in ex vivo neutralization expts. However, the high rate of variability of this antigenic fragment may play a major role in the mechanism of escape from host immune response and might represent a major obstacle to developing an HCV vaccine. Thus, even if direct exptl. evidence of the neutralizing potential of anti-HVR1 antibodies by active immunization is still missing, the generation of a vaccine candidate with a cross-reactive potential would be highly desirable. To overcome the problem of HVR1 variability, we have engineered cross-reactive HVR1 peptide mimics (mimotopes) at the N terminus of the E2 ectodomain in plasmid vectors suitable for genetic immunization. High levels of secreted and biol. active mimotope/E2 chimeras were obtained by transient transfection of these plasmids in cultured cells. All plasmids elicited anti-HVR1 antibodies in mice and rabbits with some of them leading to a cross-reacting response against many HVR1 variants from natural isolates. Epitope mapping revealed a pattern of reactivity similar to that induced by HCV infection. In contrast, plasmids encoding naturally occurring HVR1 sequences displayed either on full-length E2 in the context of the whole HCV structural region, or on a sol., secreted E2 ectodomain, did not induce a cross-reacting anti-HVR1 response.

REFERENCE COUNT: 63 THERE ARE 63 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L20 ANSWER 8 OF 11 HCAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 1999:753354 HCAPLUS

DOCUMENT NUMBER: 132:11623

TITLE: Mimotopes of **hypervariable region 1** of the **E2** glycoprotein of **hepatitis C** virus ← contains sequence 39

INVENTOR(S): **Nicosia, Alfredo; Lahm, Armin; Tramontano, Anna; Cortese, Riccardo**

PATENT ASSIGNEE(S): Istituto di Ricerche di Biologia Molecolare P. Angeletti S.P.A., Italy

SOURCE: PCT Int. Appl., 132 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE

Search completed by David Schreiber 308-4292

WO 9960132 A1 19991125 WO 1999-EP3344 19990514
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG
AU 9941435 A1 19991206 AU 1999-41435 19990514
EP 1002092 A1 20000524 EP 1999-924978 19990514
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI
PRIORITY APPLN. INFO.: GB 1998-10756 A 19980519
WO 1999-EP3344 W 19990514

AB The authors disclose peptides which are mimotopes of the **hypervariable region 1** (HVR1) of the putative envelope protein **E2** of **hepatitis C** virus (**HCV**). The phage display-derived mimotopes induce antibodies which recognize native HVR1 and are cross-reactive against different **strains** of **HCV**.

REFERENCE COUNT: 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L20 ANSWER 9 OF 11 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1999:443368 HCAPLUS
DOCUMENT NUMBER: 131:227338
TITLE: Hypervariable region 1 variants act as TCR antagonists for hepatitis C virus-specific CD4+ T cells
AUTHOR(S): Frasca, Loredana; Del Porto, Paola; Tuosto, Loretta; Marinari, Barbara; Scotta, Cristiano; Carbonari, Maurizio; **Nicosia, Alfredo**; Piccolella, Enza
CORPORATE SOURCE: Department of Cellular and Developmental Biology, "La Sapienza" University, Rome, 00185, Italy
SOURCE: Journal of Immunology (1999), 163(2), 650-658
CODEN: JOIMA3; ISSN: 0022-1767
PUBLISHER: American Association of Immunologists
DOCUMENT TYPE: Journal
LANGUAGE: English

AB In various human viral infections, the appearance of mutated epitopes displaying TCR antagonistic activity has been correlated with the severity and persistence of infection. In hepatitis C virus (HCV) infection, where the virus persistence has been assocd. with the rapid and substantial Ag modifications occurring during replication, TCR antagonism has been evidenced in CD8+ T cell responses. However, CD4+ T cell antagonism may be another important strategy by which HCV eludes a protective response, because sustained Th responses directed against several HCV Ags are assocd. with a self-limited course of infection. The data reported here represent the first evidence that variants of the hypervariable region (HVR1) of the putative Envelope 2 protein of HCV can act as powerful TCR antagonists for HVR1-specific CD4+ T cells isolated from HCV-infected individuals. Using classical antagonism assays, the authors obsd. strong inhibition of cellular proliferation and cytokine prodn. when the agonist and the antagonist ligands were simultaneously presented by the same APCs. The presence in HVR1 of conserved residues, crit. for binding to HLA-DR mols., supports the function of HVR1 variants as TCR antagonists. In conclusion, the data evidence an antagonism phenomenon, which was achieved by naturally occurring class II-restricted T cell epitopes whose mechanism

was addressed in terms of the antagonist capacity to inhibit agonist-mediated TCR down-regulation and early signal transduction.
REFERENCE COUNT: 61 THERE ARE 61 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L20 ANSWER 10 OF 11 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1998:470042 HCAPLUS
DOCUMENT NUMBER: 129:201864
TITLE: Towards a solution for hepatitis C virus hypervariability: mimotopes of the hypervariable region 1 can induce antibodies cross-reacting with a large number of viral variants
AUTHOR(S): Puntoriero, Giulia; Meola, Annalisa; **Lahm, Armin**; Zucchelli, Silvia; Ercole, Bruno Bruni; Tafi, Rosalba; Pezzanera, Monica; Mondelli, Mario U.; **Cortese, Riccardo**; **Tramontano, Anna**; Galfre, Giovanni; **Nicosia, Alfredo**
CORPORATE SOURCE: Instituto di Ricerche di Biologia Molecolare P.Angeletti, Pomezia, 00040, Italy
SOURCE: EMBO Journal (1998), 17(13), 3521-3533
CODEN: EMJODG; ISSN: 0261-4189
PUBLISHER: Oxford University Press
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The hypervariable region 1 (HVR1) of the putative envelope protein E2 of hepatitis C virus (HCV) is the most variable antigenic fragment in the whole viral genome and is mainly responsible for the large inter- and intra-individual heterogeneity of the infecting virus. It contains a principal neutralization epitope and has been proposed as the major player in the mechanism of escape from host immune response. Since anti-HVR1 antibodies are the only species shown to possess protective activity up to date, developing an effective prevention therapy is a very difficult task. The authors have approached the problem of HVR1 variability by deriving a consensus profile from >200 HVR1 sequences from different viral isolates and used it as a template to generate a vast repertoire of synthetic HVR1 surrogates displayed on M13 bacteriophage. This library was affinity selected using many different sera from infected patients. Phages were identified which react very frequently with patients' sera and bind serum antibodies that cross-react with a large panel of HVR1 peptides derived from natural HCV variants. When injected into exptl. animals, the "mimotopes" with the highest cross-reactivity induced antibodies which recognized the same panel of natural HVR1 variants. In these mimotopes the authors identified a sequence pattern responsible for the obsd. cross-reactivity. These data may hold the key for future development of a prophylactic vaccine against HCV.

L20 ANSWER 11 OF 11 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2000:317132 BIOSIS
DOCUMENT NUMBER: PREV200000317132
TITLE: Monoclonal antibodies (mAb) with broad specificity for a large repertoire of HCV variants.
AUTHOR(S): Cerino, A. (1); Meola, A.; Segagni, L. (1); Cividini, A. (1); Bruniercole, B.; Galfre, G.; **Nicosia, A.**; Mondelli, M. U. (1)
CORPORATE SOURCE: (1) Laboratori di Ricerca-Area Infettivologica, Istituto di Clinica delle Malattie Infettive, Policlinico San Matteo and University of Pavia, Pavia Italy
SOURCE: Journal of Hepatology, (2000) Vol. 32, No. Supplement 2, pp. 37. print.

Search completed by David Schreiber 308-4292

Wessendorf 09/463,098

Meeting Info.: 35th Annual Meeting of the European Association for the Study of the Liver Rotterdam, Netherlands April 29-May 03, 2000 European Association for the Study of the Liver
. ISSN: 0168-8278.
DOCUMENT TYPE: Conference
LANGUAGE: English
SUMMARY LANGUAGE: English

Search completed by David Schreiber 308-4292

! FINDPATTERNS on geneseqp:* allowing 0 mismatches

! 1 QT(T,R,H)TVGGQAS(R,H)QASSLT(S,G,R)LFS(P,L,S,Q)G(A,P,S)KQN

Databases searched:
EMBL, Release 21.0, Released on 10Oct2002, Formatted on 25Oct2002

Total finds:	0
Total length:	164,138,728
Total sequences:	908,470
CPU time:	10:16.05

! FINDPATTERNS on PIR:* allowing 0 mismatches

! 1 QT(T,R,H)TVGGQAS(R,H)QASSLT(S,G,R)LFS(P,L,S,Q)G(A,P,S)KQN

Databases searched:
NBRF, Release 73.0, Released on 16Aug2002, Formatted on 20Aug2002

Total finds:	0
Total length:	96,134,422
Total sequences:	283,224
CPU time:	02:39.40

FINDPATTERNS on Swiss-Prot:* allowing 0 mismatches

1 QT(T,R,H)TVGGQAS(R,H)QASSLT(S,G,R)LFS(P,L,S,Q)G(A,P,S)KQN

Databases searched:
SWISS-PROT, Release 40.3, Released on 9Aug2002, Formatted on 20Aug2002

Total finds:	0
Total length:	41,476,328
Total sequences:	112,892
CPU time:	01:11.37

! FINDPATTERNS on sptrembl:* allowing 0 mismatches

! 1 QT(T,R,H)TVGGQAS(R,H)QASSLT(S,G,R)LFS(P,L,S,Q)G(A,P,S)KQN

Databases searched:
SPTREMBL, Release 21.0, Released on 15Jun2002, Formatted on 28Jun2002

Total finds:	0
Total length:	206,047,115
Total sequences:	671,580
CPU time:	06:11.11

```
> O <
O| |O  IntelliGenetics
> O <

Quest - Quick User-directed Expression Search Tool
Release 5.4

                -- Outline of search "seq39iss" --

Selected search type is key against sequence data banks or files.
Selected scope is Sequence.
Selected sequence key from "wessendorf098.key":
  seq39 (AA) ID   seq39 AA preliminary pattern
1       followed by
2         qt
2         t or r or h
2         tvggqas
2         r or h
2         qasslt
2         s or g or r
2         lfs
2         p or l or s or q
2         g
2         a or p or s
2         kqn

Selected data banks and files:

   Data bank : Issued_AA , all entries

                    -- Output Parameters --

Format Options:                        File Options:
  Nucleic acid code matching   Exact     Indirect file                 No
  Find non-matching hits only  No        Sequence or key file          No
  Report key used              Yes       List of hits                  Yes
  Note position of hit         Yes       Hit display                   Yes
  Display full annotations     Yes       Name and annotations          Yes
  Sequence context             50


                      -- Run Parameters --

  Run mode                     Batch
    Time to start comparison   now
    Notify at end of run       No


No hits found.


                    -- Search Statistics --

Times:                  CPU                  Total Elapsed
                    00:03:01.09              00:05:29.00

Number of sequences searched:                  231688
Number of sequence hits:                            0
Number of separate matches:                         0
Number of sequence hits saved:                      0
```